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COMMENTARY

“Trending” statistical methods

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This is a commentary on *Ellingson et al* [2018, in this issue]: https://doi.org/10.1002/rth2.12073

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It is interesting and entertaining to us as biostatisticians that statistical analysis is subject to “fads” where investigators learn a little bit about a new statistical approach and then, as peer reviewers, recommend it be employed to get any paper accepted. The Net Reclassification Index (NRI)[1] very rapidly became extremely popular a couple of years ago; it was just impossible to do a prediction model without the argument of “but did you consider how much information it added to the prediction using NRI.” It turns out that now there is growing concern with the measure,[2–4] and the pendulum has swung where it can be a downside to reviewers when used (although these criticisms may not be completely based on an understanding of strengths and limitations of the approach[5,6]). As novel statistical approaches are developed and disseminated within the medical research community, consideration should always be taken as to whether the statistical methodology matches the research question.

Survival analysis accounting for competing causes is the new kid on the block for popular analysis requested by reviewers. The method is frequently requested to adjust for other diseases that could potentially bias estimates. Perhaps the “hottest” part of the competing risks methodology is the use of “Fine and Gray” methods[7] … a constantly recurring theme from manuscript reviewers. We suggest that many have used this methodology without knowing the underlying statistical and epidemiological nuances, specifically which components are necessary to answer different types of research questions.

We strongly recommend readers study the wonderful tutorial of these techniques by Austin and colleagues (including Fine as senior author) that points out there is not one, but rather two approaches for competing cause analysis: the Fine and Gray methods discussed above, and cause-specific analysis.[8] Additional discussion and illustration with infectious disease focus is provided by Lau et al.[9]

1. As very well-described by Austin and colleagues, the Fine and Gray methods address potential bias when the goal of the survival analysis is primarily to provide an estimate of the proportion of participants/patients that will have an event (ie, a venous thrombosis, myocardial infarction, stroke, etc.) by a certain time. For example, this would be an issue for risk functions such as the Framingham Coronary Risk Function, that provides the 10-year risk of a coronary event given demographic and risk factors.[10] Specifically, the Fine and Gray approach minimizes bias where ordinary survival models (that do not account for competing causes) will tend to overestimate the number of events. This potential of a bias becomes a greater concern if there is a separate “competing” disease with events that are: (i) related to the primary outcome of interest in the risk function analysis, and (ii) common, leading to a large number of participants/patients being removed (censored) because they have this other disease. The Fine and Gray methods can be easily implemented using most common statistical packages.
2. The other competing cause analysis is the “cause-specific analysis” that tackles a different problem of biased estimated risk coefficients from proportional hazards analysis due to removal of participants/patients by a different disease. In this case those remaining at risk for development of the disease of interest are no longer representative of those at baseline who were initially at risk for developing the disease of interest. Should this happen, the estimates from ordinary proportional hazards analysis result in biased risk estimates. Like the Fine and Gray methods, this becomes a larger concern when other diseases are both common and related to the disease of interest. The cause-specific analysis can be easily implemented by “censoring” (removing participants/patients from being at risk) when they develop the other diseases. Because of its mathematical structure, the cause-specific proportional hazards model is identical to some models ignoring competing risks.[9]

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> This cause-specific analysis focuses on the instantaneous rate of the primary event in subjects who have not yet experienced any of the events. Although further assumptions are needed to provide a direct measure of risk, the cause-specific methods still provide a valid measure of covariate effect on relative (instantaneous) hazard that participants survive all events over the observation times.[9]

It is important to note that both methods account for competing risks,[8] but they model the covariate relationships with different hazard functions. Both Austin and Lau recommend that cause-specific analytic methods are appropriate for research questions centered on disease etiology and that Fine-Gray methods are most appropriate for predicting disease incidence, individual risk and/or prognosis.

The article by Ellingsen and colleagues in this issue of RPTH appropriately employed the cause-specific analysis because of their concerns that VTE could be related to MI, stroke, cancer, or moving from the region.[11] Because MI and stroke share risk factors with VTE and are more common than VTE, this may be a valid concern. Further, cancer could be a contributor to VTE,[12] and as such failure to account for participants removed by cancer could also be a valid concern. Because the goal of the article by Ellingsen and colleagues was not to estimate the proportion of participants developing VTE, they also appropriately employed the cause-specific analysis (but not the Fine and Gray methods).

Generally, the findings of the ordinary proportional hazards analysis and the cause-specific analysis were generally concordant in this research. This demonstrates another interesting (and very fortunate) aspect of most statistical methods … that under many conditions they are surprisingly “robust” to violations of assumptions. In our experience, often when statistical assumptions are violated, many statistical methods generally provide estimates close to the correct answer. However, like Ellingsen and colleagues, the only way that this can be confirmed is to do the analysis using the alternative approach, and to present the results supporting similar findings under alternative approaches; eg the non-competing risks survival analysis with the cause-specific approach. As such, we compliment Ellingsen and colleagues for being aware of the potential that events from other diseases could bias the results in predicting VTE risk, for taking the time to appropriately apply the correct approaches to address their concerns, and for clearly presenting the results under the alternative models incorporating the cause-specific approach for addressing competing causes.

RELATIONSHIP DISCLOSURE

Drs. Howard and Long have nothing to disclose.

AUTHOR CONTRIBUTION

Drs. Howard and Long jointly wrote the commentary.

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